

## Refine Search

### Search Results -

Terms	Documents
ly333531	99

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IBM Technical Disclosure Bulletins

**Search:**

L1

**Refine Search****Recall Text****Clear****Interrupt**

### Search History

**DATE:** Friday, May 26, 2006   [Printable Copy](#)   [Create Case](#)

<u>Set Name</u> side by side	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u> result set
<i>DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=NO; OP=OR</i>			
<u>L1</u>	ly333531	99	<u>L1</u>

END OF SEARCH HISTORY

Kowluru, et al., "Diabetes-Induced Disorders of Retinal Protein Kinase C and Na, K-ATPase are Inhibited by LY333531", Abstract, American Diabetes Association Meeting Jun. 8-11, 1996.

? show files;ds;t/3,k/all

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Set	Items	Description
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S2	361	S1 NOT PD>2001
S3	175	RD (unique items)
S4	209	S1 AND PY<2001
S5	78	RD (unique items)
S6	26	S5 AND (PATIENT? OR TREAT?)
S7	31	S5 AND DIABETES
S8	14	S7 AND S6
S9	43	S7 OR S6

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S9	43	S7 OR S6

>>>KWIC option is not available in file(s): 399

9/3,K/1 (Item 1 from file: 5)  
 DIALOG(R)File 5:Biosis Previews(R)  
 (c) 2006 BIOSIS. All rts. reserv.

0012926996 BIOSIS NO.: 200100098835  
**Peripheral nerve and vascular function in diabetic rats: Effects of the beta-isoform-specific protein kinase C inhibitor \*LY333531\***  
 AUTHOR: Cotter M A (Reprint); Jack A M (Reprint); Cameron N E (Reprint)  
 AUTHOR ADDRESS: Department of Biomedical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK\*\*  
 UK  
 JOURNAL: Journal of Physiology (Cambridge) 528P p111P 2000 \*2000\*  
 MEDIUM: print  
 CONFERENCE/MEETING: Scientific Meeting of the Physiological Society Aberdeen, Scotland, UK September 06-08, 2000; 20000906  
 SPONSOR: The Physiological Society  
 ISSN: 0022-3751  
 DOCUMENT TYPE: Meeting; Meeting Abstract  
 RECORD TYPE: Citation  
 LANGUAGE: English

**Peripheral nerve and vascular function in diabetic rats: Effects of the beta-isoform-specific protein kinase C inhibitor \*LY333531\***  
 \*2000\*  
 DESCRIPTORS:  
 DISEASES: \*diabetes\*--...  
 ...endocrine disease/pancreas, metabolic disease, drug \*treatment\* effects, peripheral nerve function effects, vascular function effects  
 MESH TERMS: \*Diabetes\* Mellitus (MeSH)

9/3,K/2 (Item 2 from file: 5)  
 DIALOG(R)File 5:Biosis Previews(R)  
 (c) 2006 BIOSIS. All rts. reserv.

0012696908 BIOSIS NO.: 200000415221  
**PKC-beta inhibitor (\*LY333531\*) attenuates leukocyte entrapment in retinal microcirculation of diabetic rats**  
 AUTHOR: Nonaka Atsushi; Kiryu Junichi (Reprint); Tsujikawa Akitaka; Yamashiro Kenji; Miyamoto Kazuaki; Nishiwaki Hirokazu; Honda Yoshihito; Ogura Yuichiro  
 AUTHOR ADDRESS: Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Sakyo-ku, Kyoto, 606-8507, Japan  
 \*\*Japan  
 JOURNAL: IOVS 41 (9): p2702-2706 August, 2000 \*2000\*  
 MEDIUM: print  
 DOCUMENT TYPE: Article

RECORD TYPE: Abstract  
LANGUAGE: English

**PKC-beta inhibitor (\*LY333531\*) attenuates leukocyte entrapment in retinal microcirculation of diabetic rats**  
**\*2000\***

ABSTRACT: Purpose. The activity of protein kinase C (PKC), preferentially beta isoform of PKC, has been shown to be elevated in the diabetic retina. Recently, \*LY333531\*, a specific inhibitor of PKC-beta, has been reported to improve the decrease of retinal blood flow in early \*diabetes\*. Increased leukocyte entrapment has been suggested to be involved in blood flow disturbances in the early diabetic retina. This study was designed quantitatively to evaluate leukocyte entrapment in the retinal microcirculation of diabetic rats and the effect of \*LY333531\* on leukocyte entrapment. Methods. \*Diabetes\* was induced in male Long-Evans rats by intraperitoneal injection of streptozotocin (60 mg/kg). \*LY333531\* (0.1, 1.0, or 10.0 mg/kg/d) was administered orally during a 4-week diabetic period. Leukocyte entrapment in the retinal microcirculation...

...3 +/- 1.3 cells/mm2) was significantly increased, compared with nondiabetic control rats (7.5 +/- 0.3 cells/mm2; P < 0.0001). Oral administration of \*LY333531\* significantly decreased the number of leukocytes trapped in the retinal microcirculation of diabetic rats (10.9 +/- 0.6, 11.3 +/- 0.7, and 10.4 +/- 0.4 cells/mm2 with \*LY333531\* 0.1, 1.0, and 10.0 mg/kg/d, respectively; P < 0.05). Conclusions. \*Treatment\* with \*LY333531\* attenuated the increase of leukocyte entrapment in the retinal microcirculation during the period of early \*diabetes\*. This effect may contribute to the improvement of abnormal retinal blood flow in early \*diabetes\* with \*LY333531\*. \*LY333531\* might have a therapeutic efficacy in preventing microcirculatory flow disturbances by trapped leukocytes in the early diabetic retina.

9/3,K/3 (Item 3 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
(c) 2006 BIOSIS. All rts. reserv.

0012517462 BIOSIS NO.: 200000235775

**Salt form selection and characterization of \*LY333531\* mesylate monohydrate**

AUTHOR: Engel Gary L; Farid Nagy A; Faul Margaret M (Reprint); Richardson Lori A; Winneroski Leonard L

AUTHOR ADDRESS: Chemical Process Research and Development Division, Lilly Research Laboratories, A Division of Eli Lilly and Company, Indianapolis, IN, 46285, USA\*\*USA

JOURNAL: International Journal of Pharmaceutics (Kidlington) 198 (2): p 239-247 April 5, 2000 \*2000\*

MEDIUM: print

ISSN: 0378-5173

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

**Salt form selection and characterization of \*LY333531\* mesylate monohydrate**  
**\*2000\***

ABSTRACT: \*LY333531\* is a potent protein kinase Cbeta (PKCbeta) inhibitor currently under development for the \*treatment\* of diabetic complications. Seven salts of \*LY333531\* (hydrochloride, sulfate, mesylate, succinate, tartrate, acetate and phosphate) were evaluated

during the early phase of development. Physical property screening techniques including microscopy, DSC, TGA, XRPD...

...preferred form of the hydrochloride salt. Bioavailability studies in dogs indicated that the Cmax and area under the plasma concentration vs. time curve (AUC) for \*LY333531\* and its active metabolite, LY338522, following administration of the mesylate salt were approximately 2.6 times those obtained after the \*LY333531\* HCl dose. This difference was presumed to be due primarily to the fact that the mesylate was five times more soluble than the hydrochloride salt in water. These factors led to selection and development of \*LY333531\* mesylate monohydrate as the active pharmaceutical ingredient for clinical evaluation.

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: \*LY333531\* mesylate monohydrate...

9/3,K/4 (Item 4 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2006 BIOSIS. All rts. reserv.

0012433488 BIOSIS NO.: 200000151801

**Regulation of endothelial constitutive nitric oxide synthase gene expression in endothelial cells and in vivo: A specific vascular action of insulin**

AUTHOR: Kuboki Koji; Jiang Zhen Y; Takahara Noriko; Ha Sung Woo; Igarashi Masahiko; Yamauchi Teruaki; Feener Edward P; Herbert Terrance P; Rhodes Christopher J; King George L (Reprint)

AUTHOR ADDRESS: Joslin Diabetes Center, One Joslin Place, Boston, MA, 02215, USA\*\*USA

JOURNAL: Circulation 101 (6): p676-681 Feb. 15, 2000 \*2000\*

MEDIUM: print

ISSN: 0009-7322

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

\*2000\*

...ABSTRACT: PI-3 kinase) decreased the effect of insulin on eNOS gene expression, but a general protein kinase C (PKC) inhibitor, GF109203X or PKCbeta isoform inhibitor, \*LY333531\* enhanced eNOS expression. In contrast, PKC activators inhibited both the activation by insulin of PI-3 kinase and eNOS mRNA levels. Overexpression of PKCbeta isoform...

...in endothelial cells and microvessels. Thus, insulin may chronically modulate vascular tone. The activation of PKC in the vascular tissues as in insulin resistance and \*diabetes\* may inhibit PI-3 kinase activity and eNOS expression and may lead to endothelial dysfunctions in these pathological states.

DESCRIPTORS:

DISEASES: \*diabetes\* mellitus...

MESH TERMS: \*Diabetes\* Mellitus (MeSH...)

9/3,K/5 (Item 5 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2006 BIOSIS. All rts. reserv.

0012317694 BIOSIS NO.: 200000036007

**Enzymatic rationale and preclinical support for a potent protein kinase Cbeta inhibitor in cancer therapy**

**BOOK TITLE: Advances in Enzyme Regulation**

AUTHOR: Teicher Beverly A (Reprint); Alvarez Enrique (Reprint); Mendelsohn Laurane G (Reprint); Ara Gulshan; Menon Krishna (Reprint); Ways D Kirk (Reprint)

BOOK AUTHOR/EDITOR: Weber G (Editor)

AUTHOR ADDRESS: Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN, 46285, USA\*\*USA

SERIES TITLE: Advances in Enzyme Regulation 39 p313-327 \*1999\*

MEDIUM: print

BOOK PUBLISHER: Elsevier Science Publishers B.V., PO Box 211, Sara Burgerhartstraat 25, 1000 AE Amsterdam, The Netherlands  
Elsevier Science Publishing Co., Inc., P.O. Box 882, Madison Square Station, New York, New York 10159-2101, USA

CONFERENCE/MEETING: Thirty-ninth International Symposium on Regulation of Enzyme Activity and Synthesis in Normal and Neoplastic Tissues  
Indianapolis, Indiana, USA October 5-6, 1998; 19981005

ISSN: 0065-2571 ISBN: 0-08-043571-8

DOCUMENT TYPE: Book Chapter; Meeting; Meeting Paper

RECORD TYPE: Citation

LANGUAGE: English

\*1999\*

...REGISTRY NUMBERS: \*LY333531\*;

DESCRIPTORS:

...ORGANISMS: \*patient\*

CHEMICALS & BIOCHEMICALS: \*LY333531\*--

9/3,K/6 (Item 6 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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0012284681 BIOSIS NO.: 200000002994

**A protein kinase C-beta-selective inhibitor ameliorates neural dysfunction in streptozotocin-induced diabetic rats**

AUTHOR: Nakamura Jiro (Reprint); Kato Koichi; Hamada Yoji; Nakayama Mikihiro; Chaya Sadao; Nakashima Eitaro; Naruse Keiko; Kasuya Yasuhide; Mizubayashi Ryuichi; Miwa Kazuma; Yasuda Yutaka; Kamiya Hideki; Ienaga Kazuharu; Sakakibara Fumihiko; Koh Naoki; Hotta Nigishi

AUTHOR ADDRESS: Third Department of Internal Medicine, Nagoya University School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya, 466-8550, Japan\*\*  
Japan

JOURNAL: Diabetes 48 (10): p2090-2095 Oct., 1999 \*1999\*

MEDIUM: print

ISSN: 0012-1797

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

\*1999\*

...ABSTRACT: of PKC in diabetic neuropathy remains unclear. The present study was conducted to compare the effect of PKC inhibition by a PKC-beta-selective inhibitor, \*LY333531\* (LY), on diabetic nerve dysfunction with that of an aldose reductase inhibitor, NZ-314 (NZ). Streptozotocin-induced diabetic rats were \*treated\* with or without LY and/or NZ for 4 weeks, and motor nerve conduction velocity (MNCV), coefficient of variation of R-R interval (CVR-R...

...contents in the tail nerves were measured. Untreated diabetic rats

demonstrated delayed MNCV, decreased CVR-R, reduced SNBF, and prolonged peak latencies of oscillatory potentials. \*Treatment\* with LY as well as NZ prevented all these deficits in diabetic rats. There were no significant differences in PKC activities in membranous or cytosolic fractions of sciatic nerves between normal and diabetic rats. \*Treatment\* with neither LY nor NZ altered PKC activities. Nerve myo-inositol depletion in diabetic rats was ameliorated not only by NZ, but also by LY

...  
...REGISTRY NUMBERS: \*LY333531\*;  
DESCRIPTORS:  
CHEMICALS & BIOCHEMICALS: \*LY333531\*--

9/3,K/7 (Item 7 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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0012284680 BIOSIS NO.: 200000002993  
**Regulation of the laminin C1 promoter in cultured mesangial cells**  
AUTHOR: Phillips Stephen L; DeRubertis Fredrick R; Craven Patricia A  
(Reprint)  
AUTHOR ADDRESS: VAMC, University Dr. C, Pittsburgh, PA, 15240, USA\*\*USA  
JOURNAL: Diabetes 48 (10): p2083-2089 Oct., 1999 \*1999\*  
MEDIUM: print  
ISSN: 0012-1797  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

\*1999\*

...ABSTRACT: activity induced by culture of stable integrants in high glucose. Several inhibitors of protein kinase C, including bisindolylmaleimide (GFX), myristoylated PKC inhibitor peptide, and \*LY333531\*, were also without effect on increases in laminin C1 promoter activity induced by culture in high glucose. Exposure to the NO donor (+-)-s-nitroso-n...  
...glucose actions by the NO donor SNAP, provide potential mechanisms whereby the synthesis of the laminin gamma chain may be regulated in the glomerulus in \*diabetes\*. Of note, the mechanism by which high glucose increases laminin C1 promoter activity appears to differ from mechanisms previously described for some other glucose actions...

9/3,K/8 (Item 8 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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0012279376 BIOSIS NO.: 199900539036  
**PKC beta inhibitor prevents mesangial expansion in db/db mouse, a model for type 2 \*diabetes\***  
AUTHOR: Koya Daisuke (Reprint); Haneda Masakazu (Reprint); Nakagawa Hiroko (Reprint); Isshiki Keiji (Reprint); Sato Haruhisa; Ryuichi Ryuichi (Reprint)  
AUTHOR ADDRESS: Third Department of Medicine, Shiga University of Medical Science, Otsu, Shiga, Japan\*\*Japan  
JOURNAL: Journal of the American Society of Nephrology 10 (PROGRAM AND ABSTR. ISSUE): p684A Sept., 1999 \*1999\*  
MEDIUM: print  
CONFERENCE/MEETING: 32nd Annual Meeting of the American Society of

Nephrology Miami Beach, Florida, USA November 1-8, 1999; 19991101  
SPONSOR: American Society of Nephrology  
ISSN: 1046-6673  
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster  
RECORD TYPE: Citation  
LANGUAGE: English

**PKC beta inhibitor prevents mesangial expansion in db/db mouse, a model for  
type 2 \*diabetes\***

\*1999\*

...REGISTRY NUMBERS: \*LY333531\*

DESCRIPTORS:

...DISEASES: type 2 \*diabetes\*--

...MESH TERMS: \*Diabetes\* Mellitus, Non-Insulin-Dependent (MeSH)

CHEMICALS & BIOCHEMICALS: ...\*LY333531\*--

**9/3,K/9 (Item 9 from file: 5)**

DIALOG(R)File 5:Biosis Previews(R)

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0012220539 BIOSIS NO.: 199900480199

**Protein kinase C lies on the signaling pathway for vascular endothelial  
growth factor-mediated tumor development and angiogenesis**

AUTHOR: Yoshiji Hitoshi (Reprint); Kuriyama Shigeki; Ways D Kirk; Yoshii  
Junichi; Miyamoto Yoji; Kawata Mitsuhiro; Ikenaka Yasuhide; Tsujinoue  
Hirohisa; Nakatani Toshiya; Shibuya Masabumi; Fukui Hiroshi

AUTHOR ADDRESS: Third Department of Internal Medicine, Nara Medical  
University, 840 Shijo-cho, Kashihara, Nara, 634-8522, Japan\*\*Japan

JOURNAL: Cancer Research 59 (17): p4413-4418 Sept. 1, 1999 \*1999\*

MEDIUM: print

ISSN: 0008-5472

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

\*1999\*

...ABSTRACT: providing tetracycline in the drinking water to assess the  
tumor kinetics mediated exclusively by VEGF. In this study, we combined  
this Retro-tet system and \*LY333531\*, an inhibitor of the PKC-beta  
isoform, to elucidate the role of PKC-beta in tumor development and  
angiogenesis. Using a syngenic xenograft model, tumor...

...inhibitory effect was achieved even after the tumor was fully  
established. Immunohistochemical analysis revealed that apoptosis  
increased markedly in the tumor upon PKC-beta inhibitor \*treatment\*,  
whereas tumor cell proliferation itself did not change. Furthermore, with  
orthotopical transplantation, PKC-beta inhibition suppressed HCC tumor  
development in the liver. These results suggest...

...REGISTRY NUMBERS: \*LY333531\*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...\*LY333531\*--

**9/3,K/10 (Item 10 from file: 5)**

DIALOG(R)File 5:Biosis Previews(R)

(c) 2006 BIOSIS. All rts. reserv.

0012132974 BIOSIS NO.: 199900392634

**\*Treatment\* with the protein kinase cbeta inhibitor, \*LY333531\*, attenuates**

**the development of impaired endothelium-dependent vasodilatation in the mesenteric vasculature of diabetic rats**

AUTHOR: Jack Alison (Reprint); Cameron Norman E (Reprint); Cotter Mary A (Reprint)

AUTHOR ADDRESS: Aberdeen, UK\*\*UK

JOURNAL: Diabetes 48 (SUPPL. 1): pA130 1999 \*1999\*

MEDIUM: print

CONFERENCE/MEETING: 59th Scientific Sessions of the American Diabetes Association San Diego, California, USA June 19-22, 1999; 19990619

SPONSOR: American Diabetes Association

ISSN: 0012-1797

DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster

RECORD TYPE: Citation

LANGUAGE: English

**\*Treatment\* with the protein kinase cbeta inhibitor, \*LY333531\*, attenuates the development of impaired endothelium-dependent vasodilatation in the mesenteric vasculature of diabetic rats**

**\*1999\***

...REGISTRY NUMBERS: \*LY333531\*

DESCRIPTORS:

DISEASES: \*diabetes\*--

MESH TERMS: \*Diabetes\* Mellitus (MeSH)

CHEMICALS & BIOCHEMICALS: ...\*LY333531\*--

**9/3,K/11 (Item 11 from file: 5)**

DIALOG(R)File 5:Biosis Previews(R)

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0012104616 BIOSIS NO.: 199900364276

**Widespread vascular barrier dysfunction induced by \*diabetes\* and by \*LY333531\*, a beta-selective inhibitor of protein kinase C**

AUTHOR: Williamson Joseph R (Reprint); Ido Yasuo (Reprint); Chang Kathy (Reprint)

AUTHOR ADDRESS: Saint Louis, MO, USA\*\*USA

JOURNAL: Diabetes 48 (SUPPL. 1): pA97-A98 1999 \*1999\*

MEDIUM: print

CONFERENCE/MEETING: 59th Scientific Sessions of the American Diabetes Association San Diego, California, USA June 19-22, 1999; 19990619

SPONSOR: American Diabetes Association

ISSN: 0012-1797

DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster

RECORD TYPE: Citation

LANGUAGE: English

**Widespread vascular barrier dysfunction induced by \*diabetes\* and by \*LY333531\*, a beta-selective inhibitor of protein kinase C**

**\*1999\***

...REGISTRY NUMBERS: \*LY333531\*

DESCRIPTORS:

...ORGANISMS: \*patient\*

DISEASES: \*diabetes\*--

MESH TERMS: \*Diabetes\* Mellitus (MeSH)

CHEMICALS & BIOCHEMICALS: ...\*LY333531\*--

**9/3,K/12 (Item 12 from file: 5)**

DIALOG(R)File 5:Biosis Previews(R)

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0012070913 BIOSIS NO.: 199900330573

**Protein kinase C beta-selective inhibitor \*LY333531\* ameliorates abnormal retinal hemodynamics in \*patients\* with \*diabetes\***

AUTHOR: Aiello Lloyd Paul (Reprint); Bursell Sven (Reprint); Devries Todd (Reprint); Alatorre Carlos (Reprint); King George (Reprint); Ways Kirk (Reprint)

AUTHOR ADDRESS: Boston, MA, USA\*\*USA

JOURNAL: Diabetes 48 (SUPPL. 1): pA19 1999 \*1999\*

MEDIUM: print

CONFERENCE/MEETING: 59th Scientific Sessions of the American Diabetes Association San Diego, California, USA June 19-22, 1999; 19990619

SPONSOR: American Diabetes Association

ISSN: 0012-1797

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

**Protein kinase C beta-selective inhibitor \*LY333531\* ameliorates abnormal retinal hemodynamics in \*patients\* with \*diabetes\***

\*1999\*

...REGISTRY NUMBERS: \*LY333531\*

DESCRIPTORS:

...ORGANISMS: \*patient\*

DISEASES: \*diabetes\*--

MESH TERMS: \*Diabetes\* Mellitus (MeSH...

CHEMICALS & BIOCHEMICALS: \*LY333531\*--

9/3,K/13 (Item 13 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2006 BIOSIS. All rts. reserv.

0012028716 BIOSIS NO.: 199900288376

**Basic fibroblast growth factor induces expression of VEGF receptor KDR through a protein kinase C and p44/p42 mitogen-activated protein kinase-dependent pathway**

AUTHOR: Hata Yasuaki; Rook Susan L; Aiello Lloyd Paul (Reprint)

AUTHOR ADDRESS: Joslin Diabetes Center, One Joslin Place, Boston, MA, 02215, USA\*\*USA

JOURNAL: Diabetes 48 (5): p1145-1155 May, 1999 \*1999\*

MEDIUM: print

ISSN: 0012-1797

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

\*1999\*

...ABSTRACT: that inhibited bFGF-induced MAPK phosphorylation 100%, suggesting that pathways in addition to MAPK might also be involved. Inhibitors of the beta isoform of PKC (\*LY333531\*), protein kinase A (PKA) (H89), and phosphatidylinositol (PI) 3 kinase (wortmannin) had no significant effect. These data suggest that bFGF stimulates KDR expression through a...

DESCRIPTORS:

DISEASES: \*diabetes\*--

MESH TERMS: \*Diabetes\* Mellitus (MeSH)

content by Western blot, immunohistochemistry, enzymatic activity, and in situ hybridization...

...PKC activity was significantly increased in membrane fractions from failed hearts compared with nonfailed (1021 +/- 189 versus 261 +/- 89 pmolcntdotmg-1cntdotmin-1, P < 0.01). \*LY333531\*, a selective PKC-beta inhibitor, significantly decreased PKC activity in membrane fractions from failed hearts by 209 pmolcntdotmin-1cntdotmg-1 (versus 42.5 pmolcntdotmin-1cntdotmg-1).

DESCRIPTORS:

...ORGANISMS: \*patient\*

9/3,K/18 (Item 18 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2006 BIOSIS. All rts. reserv.

0011631118 BIOSIS NO.: 199800425365

**\*LY333531\* single escalating oral dose study in healthy volunteers**

AUTHOR: Demolle D; De Suray J M; Vandenhende F; Onkelinx C

AUTHOR ADDRESS: Lilly Development Centre, 11 rue Granbonpre, 1348 Mont-Saint-Guibert, Belgium\*\*Belgium

JOURNAL: Diabetologia 41 (SUPPL. 1): pA283 Aug., 1998 \*1998\*

MEDIUM: print

CONFERENCE/MEETING: 34th Annual Meeting of the European Association for the Study of Diabetes Barcelona, Spain September 11, 199819980911

SPONSOR: European Association for the Study of Diabetes

ISSN: 0012-186X

DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster

RECORD TYPE: Citation

LANGUAGE: English

**\*LY333531\* single escalating oral dose study in healthy volunteers**

\*1998\*

...REGISTRY NUMBERS: \*LY333531\*

DESCRIPTORS:

...ORGANISMS: \*patient\*

DISEASES: \*diabetes\* mellitus...

MESH TERMS: \*Diabetes\* Mellitus (MeSH...

CHEMICALS & BIOCHEMICALS: ...\*LY333531\*--

9/3,K/19 (Item 19 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2006 BIOSIS. All rts. reserv.

0011630233 BIOSIS NO.: 199800424480

**Effects of the protein kinase Cbeta inhibitor, \*LY333531\*, on nerve and vascular function in diabetic rats**

AUTHOR: Cameron N E (Reprint); Jack A (Reprint); Ways D K; Cotter M A (Reprint)

AUTHOR ADDRESS: Biomedical Sci., Aberdeen Univ., Aberdeen, UK\*\*UK

JOURNAL: Diabetologia 41 (SUPPL. 1): pA54 Aug., 1998 \*1998\*

MEDIUM: print

CONFERENCE/MEETING: 34th Annual Meeting of the European Association for the Study of Diabetes Barcelona, Spain September 11, 199819980911

SPONSOR: European Association for the Study of Diabetes

ISSN: 0012-186X

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

**Effects of the protein kinase Cbeta inhibitor, \*LY333531\*, on nerve and vascular function in diabetic rats**

\*1998\*

...REGISTRY NUMBERS: \*LY333531\*

DESCRIPTORS:

DISEASES: \*diabetes\*--

MESH TERMS: \*Diabetes\* Mellitus (MeSH)

CHEMICALS & BIOCHEMICALS: ...\*LY333531\*--

9/3,K/20 (Item 20 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2006 BIOSIS. All rts. reserv.

0011391121 BIOSIS NO.: 199800185368

**Inhibition of intraocular neovascularization caused by retinal ischemia in pigs by PKCbeta inhibition with \*LY333531\***

AUTHOR: Danis Ronald P (Reprint); Bingaman David P; Jirousek Michael; Yang Yishuang

AUTHOR ADDRESS: Dep. Ophthalmol., 702 Rotary Circle, Indianapolis, IN 46202, USA\*\*USA

JOURNAL: IOVS 39 (1): p171-179 Jan., 1998 \*1998\*

MEDIUM: print

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

**Inhibition of intraocular neovascularization caused by retinal ischemia in pigs by PKCbeta inhibition with \*LY333531\***

\*1998\*

ABSTRACT: OBJECTIVE. The authors tested the antiangiogenic properties of an orally administered protein kinase-Cbeta inhibitor, \*LY333531\*, in a pig model of preretinal neovascularization caused by retinal branch vein occlusion to determine the effectiveness of this therapy in preventing intraocular neovascularization from...

...standardized manner using photodynamic thrombosis with rose bengal dye and thermal burns from an argon laser with green light. Five animals received 1 mg/kg \*LY333531\* daily in two oral doses, and five animals were untreated. The eyes were followed clinically for 12 weeks with ophthalmoscopy, fundus photography, and fluorescein angiography...

...the unpaired data between the two eyes of each animal (data were rounded up). RESULTS. Significant inhibition of neovascularization was observed in eyes from animals \*treated\* with the study drug (P = 0.03). Although some of the \*treated\* eyes demonstrated no clinically evident new vessels, histopathologic and photographic analysis demonstrated fine new vessels on the optic disc in all eyes (mean grade 1...

...evident neovascularization (mean grade 3.1). The oral drug was well tolerated, and no side effects were documented. CONCLUSIONS. A specific protein kinase-Cbeta inhibitor, \*LY333531\*, effectively inhibited preretinal and optic nerve head neovascularization in the pig model of branch retinal vein occlusion. This was consistent with the known pathways of signal transduction by growth factors in activated cells and suggested that inhibition of this key regulatory isozyme is effective in the \*treatment\* of ischemia-mediated neovascular diseases.

...REGISTRY NUMBERS: \*LY333531\*

DESCRIPTORS:

**Effects of the protein kinase Cbeta inhibitor, \*LY333531\*, on nerve and vascular function in diabetic rats**

\*1998\*

...REGISTRY NUMBERS: \*LY333531\*

DESCRIPTORS:

DISEASES: \*diabetes\*--

MESH TERMS: \*Diabetes\* Mellitus (MeSH)

CHEMICALS & BIOCHEMICALS: ...\*LY333531\*--

9/3,K/20 (Item 20 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2006 BIOSIS. All rts. reserv.

0011391121 BIOSIS NO.: 199800185368

**Inhibition of intraocular neovascularization caused by retinal ischemia in pigs by PKCbeta inhibition with \*LY333531\***

AUTHOR: Danis Ronald P (Reprint); Bingaman David P; Jirousek Michael; Yang Yishuang

AUTHOR ADDRESS: Dep. Ophthalmol., 702 Rotary Circle, Indianapolis, IN 46202, USA\*\*USA

JOURNAL: IOVS 39 (1): p171-179 Jan., 1998 \*1998\*

MEDIUM: print

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

**Inhibition of intraocular neovascularization caused by retinal ischemia in pigs by PKCbeta inhibition with \*LY333531\***

\*1998\*

ABSTRACT: OBJECTIVE. The authors tested the antiangiogenic properties of an orally administered protein kinase-Cbeta inhibitor, \*LY333531\*, in a pig model of preretinal neovascularization caused by retinal branch vein occlusion to determine the effectiveness of this therapy in preventing intraocular neovascularization from...

...standardized manner using photodynamic thrombosis with rose bengal dye and thermal burns from an argon laser with green light. Five animals received 1 mg/kg \*LY333531\* daily in two oral doses, and five animals were untreated. The eyes were followed clinically for 12 weeks with ophthalmoscopy, fundus photography, and fluorescein angiography...

...the unpaired data between the two eyes of each animal (data were rounded up). RESULTS. Significant inhibition of neovascularization was observed in eyes from animals \*treated\* with the study drug (P = 0.03). Although some of the \*treated\* eyes demonstrated no clinically evident new vessels, histopathologic and photographic analysis demonstrated fine new vessels on the optic disc in all eyes (mean grade 1...

...evident neovascularization (mean grade 3.1). The oral drug was well tolerated, and no side effects were documented. CONCLUSIONS. A specific protein kinase-Cbeta inhibitor, \*LY333531\*, effectively inhibited preretinal and optic nerve head neovascularization in the pig model of branch retinal vein occlusion. This was consistent with the known pathways of signal transduction by growth factors in activated cells and suggested that inhibition of this key regulatory isozyme is effective in the \*treatment\* of ischemia-mediated neovascular diseases.

...REGISTRY NUMBERS: \*LY333531\*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: \*LY333531\*--

9/3,K/21 (Item 21 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
(c) 2006 BIOSIS. All rts. reserv.

0011369774 BIOSIS NO.: 199800164021

**Abnormalities of retinal metabolism in \*diabetes\* or experimental**

**galactosemia: V. Relationship between protein kinase C and ATPases**  
AUTHOR: Kowluru Renu A (Reprint); Jirousek Michael R; Stramm Lawrence;  
Farid Nagy; Engerman Ronald L; Kern Timothy S  
AUTHOR ADDRESS: Dep. Ophthalmol. Visual Sci., Med. Sci. Cent., Univ.  
Wisconsin, 1300 University Ave., Madison, WI 53706-1532, USA\*\*USA  
JOURNAL: Diabetes 47 (3): p464-469 March, 1998 \*1998\*  
MEDIUM: print  
ISSN: 0012-1797  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

**Abnormalities of retinal metabolism in \*diabetes\* or experimental**  
**galactosemia: V. Relationship between protein kinase C and ATPases**  
\*1998\*

...ABSTRACT: retinopathy, experimental galactosemia. We have investigated the relationship between hyperglycemia-induced abnormalities of PKC and ATPases using a selective inhibitor of beta isoform of PKC (\*LY333531\*). \*Diabetes\* or experimental galactosemia of 2 months' duration resulted in >50% elevation of PKC activity in the retina, and administration of \*LY333531\* prevented the elevation. In retinas of the same rats, the \*LY333531\* prevented hyperglycemia-induced decreases of both Na<sup>+</sup>-K<sup>+</sup>-ATPase and calcium ATPase activities. Retinal microvessels, the main site of lesions in diabetic retinopathy, likewise showed elevated activity of PKC and inhibition of ATPases in \*diabetes\* and in experimental galactosemia, and administration of \*LY333531\* to diabetic animals prevented these abnormalities. PKC activity in sciatic nerves, in contrast, became subnormal in \*diabetes\* and experimental galactosemia, and \*LY333531\* had no effect on PKC activity in the sciatic nerve. PKC activity in the cerebral cortex was not affected by \*diabetes\* or experimental galactosemia. The results suggest that \*diabetes\*-induced reductions in Na<sup>+</sup>-K<sup>+</sup>-ATPase and calcium ATPase in the retina are mediated in large part by PKC-beta. The availability of an agent...

DESCRIPTORS:

DISEASES: \*diabetes\*--  
MESH TERMS: \*Diabetes\* Mellitus (MeSH...

9/3,K/22 (Item 22 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
(c) 2006 BIOSIS. All rts. reserv.

0011345817 BIOSIS NO.: 199800140064

**Mechanisms of insulin resistance and new pharmacological approaches to**  
**metabolism and diabetic complications**

AUTHOR: Donnelly Richard (Reprint); Qu Xianqin  
AUTHOR ADDRESS: Div. Vascular Med., Univ. Nottingham, Derbyshire Royal  
Infirmary, Derby DE1 2QY, UK\*\*UK  
JOURNAL: Clinical and Experimental Pharmacology and Physiology 25 (2): p  
79-87 Feb., 1998 \*1998\*  
MEDIUM: print

ISSN: 0305-1870  
DOCUMENT TYPE: Article; Literature Review  
RECORD TYPE: Abstract  
LANGUAGE: English

\*1998\*

ABSTRACT: 1. Resistance to insulin-mediated glucose transport and metabolism has been identified as a primary mechanism in the pathogenesis of non-insulin-dependent \*diabetes\* mellitus (NIDDM) and as a target for drug development. The aetiology of insulin resistance is likely to be multifactorial, but the present review focuses on...

...of insulin resistance. In addition, there is separate evidence that glucose-induced PKC activation plays an important role in the micro- and macrovascular complications of \*diabetes\*. 3. New pharmacological approaches to NIDDM and obesity have focused on insulin-sensitizing agents (e.g. troglitazone), beta3-AR agonists, anti-lipolytic drugs (e.g. the adenosine A1 receptor agonist GR79236) and selective inhibitors of PKC isoforms (e.g. the inhibitor of PKC-beta \*LY333531\*). Experimental studies with GR79236 show that this drug ameliorates the by pertriglyceridaemia induced by fructose feeding and that the reduction in fatty acid levels is...

...REGISTRY NUMBERS: \*LY333531\*

DESCRIPTORS:

DISEASES: non-insulin-dependent \*diabetes\* mellitus...

MESH TERMS: \*Diabetes\* Mellitus, Non-Insulin-Dependent (MeSH...

CHEMICALS & BIOCHEMICALS: ...\*LY333531\*--

9/3,K/23 (Item 23 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2006 BIOSIS. All rts. reserv.

0011291798 BIOSIS NO.: 199800086045

**Specific retinal diacylglycerol and protein kinase C beta isoform modulation mimics abnormal retinal hemodynamics in diabetic rats**

AUTHOR: Bursell Sven-Erik (Reprint); Takagi Chikako; Clermont Allen C; Takagi Hitoshi; Mori Fumihiko; Ishii Hidehiro; King George L

AUTHOR ADDRESS: Beetham Eye Inst., Joslin Diabetes Cent., One Joslin Place, Boston, MA 02215, USA\*\*USA

JOURNAL: Investigative Ophthalmology and Visual Science 38 (13): p 2711-2720 Dec., 1997 \*1997\*

MEDIUM: print

ISSN: 0146-0404

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

\*1997\*

...ABSTRACT: abnormalities of retinal and renal hemodynamics. The object of this study was to determine whether direct elevation of retinal DAG levels, in the absence of \*diabetes\* or hyperglycemia, can mimic the hemodynamic abnormalities normally observed in diabetic rats. Retinal DAG levels were elevated using an inhibitor of DAG kinase that converts DAG to phosphatidic acid. The effectiveness of a specific PKC-beta isoform inhibitor introduced directly into the retinas of diabetic rats in reversing \*diabetes\*-related abnormal retinal hemodynamics was also investigated. Methods. For retinal blood flow studies, diacylglycerol kinase (DGK) inhibitor R59949, at various concentrations, was injected into the vitreous of nondiabetic Sprague-Dawley rats (n = 33), and a

PKC-beta isoform-selective inhibitor \*LY333531\* was injected into the vitreous of rats with streptozotocin (STZ)-induced \*diabetes\* of 2 weeks' duration (n = 21). Retinal hemodynamic changes were quantitated using video-based fluorescein angiography. Total DAG levels were assayed from five nondiabetic rat...

...sustained for 60 minutes after injection. These retinal hemodynamic parameters after DGK inhibition were comparable to those measured at baseline in rats with STZ-induced \*diabetes\* of 2 weeks' duration (MCT = 1.38 +/- 0.20 seconds; retinal blood flow = 68 +/- 11.2 pixel2/second). Intravitreal injection of the PKC-beta inhibitor (\*LY333531\*) at 10<sup>-5</sup> M in diabetic rats decreased by a factor of 1.6 the \*diabetes\*-related increased PKC activation, decreased the prolonged MCT (0.98 +/- 0.13 seconds; P < 0.01) and increased retinal blood flow (93.4 +/- 14.2...

DESCRIPTORS:

DISEASES: \*diabetes\*--

MESH TERMS: \*Diabetes\* Mellitus (MeSH)

9/3,K/24 (Item 24 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2006 BIOSIS. All rts. reserv.

0011281286 BIOSIS NO.: 199800075533

**Protein kinase C activation and its role in the development of vascular complications in \*diabetes\* mellitus**

AUTHOR: Ishii Hidehiro; Koya Daisuke; King George L (Reprint)

AUTHOR ADDRESS: Res. Div., Joslin Diabetes Cent., Dep. Internal Med., Brigham and Women's Hosp., Harvard Med. Sch., One Joslin Place, Boston, MA 02215, USA\*\*USA

JOURNAL: Journal of Molecular Medicine (Berlin) 76 (1): p21-31 Jan., 1998  
\*1998\*

MEDIUM: print

ISSN: 0946-2716

DOCUMENT TYPE: Article; Literature Review

RECORD TYPE: Abstract

LANGUAGE: English

**Protein kinase C activation and its role in the development of vascular complications in \*diabetes\* mellitus**

\*1998\*

...ABSTRACT: isoforms of PKC predominantly the beta isoforms are activated in cultured vascular cells exposed to high glucose and vascular tissues isolated from animal models of \*diabetes\* mellitus. Administration of vitamin E, which decreases DAG level possibly through the activation of DAG kinase, prevents hemodynamic changes in retina and renal glomeruli of diabetic rats. In addition, the inhibition of PKC beta isoforms by a specific inhibitor (\*LY333531\*) can normalize the changes in gene expression of cytokines, caldesmon, and hemodynamics. These results provide supportive evidence that the activation of PKC, especially the beta isoforms, is involved in the development of diabetic vascular complications, and that PKCbeta inhibitors can be used in the \*treatment\* of diabetic vascular complications.

DESCRIPTORS:

...ORGANISMS: \*patient\*

DISEASES: \*diabetes\* mellitus...

MESH TERMS: \*Diabetes\* Mellitus (MeSH)

9/3,K/25 (Item 25 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)  
(c) 2006 BIOSIS. All rts. reserv.

0011032883 BIOSIS NO.: 199799666943

**Characterization of protein kinase C beta isoform activation on the gene expression of transforming growth factor-beta, extracellular matrix components, and prostanoids in the glomeruli of diabetic rats**

AUTHOR: Koya Daisuke; Jirousek Michael R; Lin You-Wei; Ishii Hidehiro; Kuboki Koji; King George L (Reprint)

AUTHOR ADDRESS: Joslin Diabetes Cent., One Joslin Place, Boston, MA 02215, USA\*\*USA

JOURNAL: Journal of Clinical Investigation 100 (1): p115-126 1997 \*1997\*

ISSN: 0021-9738

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

\*1997\*

...ABSTRACT: protein kinase C (PKC) pathway in the vascular tissues by hyperglycemia has been associated with many of the cellular changes observed in the complications of \*diabetes\*. Recently, we have reported that the use of a novel, orally effective specific inhibitor of PKC beta isoform (\*LY333531\*) normalized many of the early retinal and renal hemodynamics in rat models of \*diabetes\*. In the present study, we have characterized a spectrum of biochemical and molecular abnormalities associated with chronic changes induced by glucose or \*diabetes\* in the cultured mesangial cells and renal glomeruli that can be prevented by \*LY333531\*. Hyperglycemia increased diacylglycerol (DAG) level in cultured mesangial cells exposed to high concentrations of glucose and activated PKC alpha- and beta-1 isoforms in the renal glomeruli of diabetic rats. The addition of PKC beta selective inhibitor (\*LY333531\*) to cultured mesangial cells inhibited activated PKC activities by high glucose without lowering DAG levels and \*LY333531\* given orally in diabetic rats specifically inhibited the activation of PKC beta-1 isoform without decreasing PKC alpha isoform activation. Glucose-induced increases in arachidonic acid release, prostaglandin E-2 production, and inhibition of Na<sup>+</sup>-K<sup>+</sup> ATPase activities in the cultured mesangial cells were completely prevented by the addition of \*LY333531\*. Oral feeding of \*LY333531\* prevented the increased mRNA expression of TGF-beta-1 and extracellular matrix components such as fibronectin and alpha-1(IV) collagen in the glomeruli of...

DESCRIPTORS:

MISCELLANEOUS TERMS: ...\*DIABETES\*;

9/3,K/26 (Item 26 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)  
(c) 2006 BIOSIS. All rts. reserv.

0010836258 BIOSIS NO.: 199799470318

**Mechanisms of glucose toxicity. New hope for prevention of diabetic complications?**

AUTHOR: Dutour Anne

AUTHOR ADDRESS: UFR de Medecine Nord, Boulevard Pierre Dramard, F-13916 Marseille Cedex 20, France\*\*France

JOURNAL: European Journal of Endocrinology 136 (1): p39-40 1997 \*1997\*

ISSN: 0804-4643

DOCUMENT TYPE: Article

RECORD TYPE: Citation

LANGUAGE: English

\*1997\*

...REGISTRY NUMBERS: \*LY333531\*;

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...\*LY333531\*;

MISCELLANEOUS TERMS: ...\*LY333531\*;

...\*PATIENT\*;

9/3,K/27 (Item 27 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2006 BIOSIS. All rts. reserv.

0010458857 BIOSIS NO.: 199699092917

(S)-13-((Dimethylamino)methyl)-10,11,14,15-tetrahydro-4,9:16,21-dimetheno-1H,13H-dibenzo(e,k)pyrrolo(3,4-h)(1,4,13)oxadiazacyclohexadecene-1,3(2H)-dione (\*LY333531\*) and related analogues: Isozyme selective inhibitors of protein kinase C-beta

AUTHOR: Jirousek Michael R (Reprint); Gillig James R; Gonzalez Cecile M; Heath William F; McDonald John H II; Neel David A; Rito Christopher J; Singh Upinder; Stramm Lawrence E; Melikian-Badalian Anita; Baevsky Matthew; Ballas Lawrence M; Hall Steven E; Winneroski Leonard L; Paul Margaret M

AUTHOR ADDRESS: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN 46285, USA\*\*USA

JOURNAL: Journal of Medicinal Chemistry 39 (14): p2664-2671 1996 \*1996\*

ISSN: 0022-2623

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

...

14,15-tetrahydro-4,9:16,21-dimetheno-1H,13H-dibenzo(e,k)pyrrolo(3,4-h)(1,4,13)oxadiazacyclohexadecene-1,3(2H)-dione (\*LY333531\*) and related analogues: Isozyme selective inhibitors of protein kinase C-beta

\*1996\*

...ABSTRACT: I, beta-II, gamma, delta, epsilon, zeta, eta) was used to identify the series and optimize the structure and associated activity relationship. The dimethylamine analogue \*LY333531\* (1), (S)-13-((dimethylamino)methyl)-10,11,14,15-tetrahydro-4,9:16,21-dimetheno-1H,13H-dibenzo(e,k)pyrrolo(3,4-h)(1...

...I and PKC-beta-II in comparison to PKC-alpha, respectively. The additional analogues described in the series are also selective inhibitors of PKC-beta. \*LY333531\* (1) exhibits ATP dependent competitive inhibition of PKC-beta-I and is selective for PKC in comparison to other ATP dependent kinases (protein kinase A...

...REGISTRY NUMBERS: \*LY333531\*

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...\*LY333531\*

MISCELLANEOUS TERMS: ...\*DIABETES\*;

...\*LY333531\*; \*LY333531\* ANALOGUES

9/3,K/28 (Item 28 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2006 BIOSIS. All rts. reserv.

0010352106 BIOSIS NO.: 199698819939

**Amelioration of vascular dysfunctions in diabetic rats by an oral PKC beta inhibitor**

AUTHOR: Ishii Hidehiro; Jirousek Michael R; Koya Daisuke; Takagi Chikako; Xia Pu; Clermont Allen; Bursell Sven-Erik; Kern Timothy S; Ballas Lawrence M; Heath William F; Stramm Lawrence E; Feener Edward P; King George L (Reprint)

AUTHOR ADDRESS: Res. Div., Joslin Diabetes Cent., Dep. Med., Brigham, Women's Hosp., Harvard Med. Sch., 1 Joslin Place, Boston, MA 02215, USA\*\*  
USA

JOURNAL: Science (Washington D C) 272 (5262): p728-731 1996 \*1996\*

ISSN: 0036-8075

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

\*1996\*

ABSTRACT: The vascular complications of \*diabetes\* mellitus have been correlated with enhanced activation of protein kinase C (PKC). \*LY333531\*, a specific inhibitor of the beta isoform of PKC, was synthesized and was shown to be a competitive reversible inhibitor of PKC beta-1 and...

...5 nM; this value was one-fiftieth of that for other PKC isoenzymes and one-thousandth of that for non-PKC kinases. When administered orally, \*LY333531\* ameliorated the glomerular filtration rate, albumin excretion rate, and retinal circulation in diabetic rats in a dose-responsive manner, in parallel with its inhibition of...

9/3,K/29 (Item 1 from file: 24)

DIALOG(R)File 24:CSA Life Sciences Abstracts

(c) 2006 CSA. All rts. reserv.

0002030644 IP ACCESSION NO: 4604535

**Protein Kinase C in the \*Treatment\* of Disease: Signal Transduction Pathways, Inhibitors, and Agents in Development**

Goekjian, PG; Jirousek, MR

Mississippi State University, Mississippi State, Mississippi 39762, USA

Current Medicinal Chemistry, v 6, n 9, p 877-903, 1999

PUBLICATION DATE: \*1999\*

DOCUMENT TYPE: Journal Article; Review

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ISSN: 0929-8673

FILE SEGMENT: Medical & Pharmaceutical Biotechnology Abstracts

**Protein Kinase C in the \*Treatment\* of Disease: Signal Transduction Pathways, Inhibitors, and Agents in Development**

PUBLICATION DATE: \*1999\*

ABSTRACT:

... A survey of the current generation of potent and selective ATP-competitive inhibitors is provided. The progress of PKC inhibitors currently in clinical development, including \*LY333531\*, ISIS 3521 (CGP 64128A), bryostatin 1, GF109203x, Ro 32-0432 and Ro 31-8220, Go 6976 and Go 7611, CPR 1006, and balanol (SPC 100840...

9/3,K/30 (Item 1 from file: 34)  
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci  
(c) 2006 Inst for Sci Info. All rts. reserv.

09166056 Genuine Article#: 374TX No. References: 193  
**Title: Protein kinase C activation and its pharmacological inhibition in vascular disease**  
Author(s): Meier M; King GL (REPRINT)  
Corporate Source: 1 JOSLIN PL,/BOSTON//MA/02215 (REPRINT); HARVARD UNIV,SCH MED, JOSLIN DIABET CTR, DIV RES/BOSTON//MA/02115  
Journal: VASCULAR MEDICINE, \*2000\*, V5, N3 (AUG), P173-185  
ISSN: 1358-863X Publication date: 20000800  
Publisher: ARNOLD, HODDER HEADLINE PLC, 338 EUSTON ROAD, LONDON NW1 3BH, ENGLAND  
Language: English Document Type: REVIEW (ABSTRACT AVAILABLE)

, \*2000\*  
Abstract: Vascular complications in \*diabetes\* mellitus are known to be associated with the activation of the protein kinase C (PKC) pathway through the de novo synthesis of diacylglycerol (DAG) from...  
...proliferation, induces the activation of cytosolic phospholipase A(2) and inhibits the activity of Na+K+-ATPase. These events are not only frequently observed in \*diabetes\* mellitus but are also involved in the actions of vasoactive agents or oxidative stress. Inhibition of PKC by two different kinds of PKC inhibitors - \*LY333531\*, a selective PKC-p-isoform inhibitor, and vitamin E, d-alpha-tocopheron -were able to prevent or reverse the various vascular dysfunctions in vitro and...  
...Clinical studies using these compounds are now ongoing to evaluate the significance of DAG-PKC pathway activation in the development of vascular complications in diabetic \*patients\*.  
...Identifiers--NITRIC-OXIDE SYNTHASE; GLOMERULAR MESANGIAL CELLS; GROWTH-FACTOR-BETA; DEPENDENT \*DIABETES\*-MELLITUS; SMOOTH-MUSCLE CELLS; RETINAL BLOOD-FLOW; ELEVATED GLUCOSE-LEVELS; MESSENGER-RNA EXPRESSION; SODIUM-POTASSIUM-ATPASE; HUMAN ENDOTHELIAL-CELLS

9/3,K/31 (Item 2 from file: 34)  
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci  
(c) 2006 Inst for Sci Info. All rts. reserv.

07929050 Genuine Article#: 225QU No. References: 29  
**Title: The role of protein kinase C activation in the pathogenesis of diabetic vascular complications**  
Author(s): Park JY; Ha SW; King GL (REPRINT)  
Corporate Source: HARVARD UNIV,SCH MED, DIV RES, JOSLIN DIABET CTR/BOSTON//MA/02215 (REPRINT); HARVARD UNIV,SCH MED, DIV RES, JOSLIN DIABET CTR/BOSTON//MA/02215  
Journal: PERITONEAL DIALYSIS INTERNATIONAL, \*1999\*, V19, 2, PS222-S227  
ISSN: 0896-8608 Publication date: 19990000  
Publisher: MULTIMED INC, 66 MARTIN ST, TORONTO ON L9T 2R2, CANADA  
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

, \*1999\*  
Abstract: Many vascular diseases in \*diabetes\* are known to be associated with the activation of the diacylglycerol (DAG)protein kinase C (PKC) pathway. The major source of DAG that is elevated in \*diabetes\* is de novo synthesis from glycolytic intermediates. Among the various PKC

isoforms, the p-isoform has been shown to be persistently activated in diabetic animals. Multiple lines of evidence have shown that many vascular alterations in \*diabetes\* - such as a decrease in the activity of Na<sup>+</sup>-K<sup>+</sup>-adenosine triphosphatase (Na<sup>+</sup>-K<sup>+</sup>-ATPase), and increases in extracellular matrix, cytokines, permeability, contractility, and cell proliferation - are caused by activation of PKC. Inhibition of PKC by two different kinds of PKC inhibitors, \*LY333531\*, a selective PKC-P-isoform inhibitor, and d-alpha-tocopherol, were able to prevent or reverse the various vascular dysfunctions in diabetic rats. These results have also provided in vivo evidence that DAG-PKC activation could be responsible for the hyperglycemia-induced vascular dysfunctions in \*diabetes\*. Clinical studies are now being performed to clarify the pathogenic roles of the DAG-PKC pathway in developing vascular complications in diabetic \*patients\*.

9/3,K/32 (Item 3 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci  
(c) 2006 Inst for Sci Info. All rts. reserv.

07777064 Genuine Article#: 194VR No. References: 0

**Title: \*Treatment\* with the protein kinase C beta inhibitor, \*LY333531\*,  
attenuates the development of impaired endothelium-dependent  
vasodilatation in the mesenteric vasculature of diabetic rats**

Author(s): Jack A; Cameron ME; Cotter MA

Journal: DIABETES, \*1999\*, V48, 1, P558-558

ISSN: 0012-1797 Publication date: 19990000

Publisher: AMER DIABETES ASSOC, 1660 DUKE ST, ALEXANDRIA, VA 22314

Language: English Document Type: MEETING ABSTRACT

**Title: \*Treatment\* with the protein kinase C beta inhibitor, \*LY333531\*,  
attenuates the development of impaired endothelium-dependent  
vasodilatation in the mesenteric vasculature of diabetic rats**  
, \*1999\*

9/3,K/33 (Item 4 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci  
(c) 2006 Inst for Sci Info. All rts. reserv.

04831191 Genuine Article#: UJ883 No. References: 0

**Title: \*DIABETES\*-INDUCED DISORDERS OF RETINAL PROTEIN-KINASE-C AND  
NA,K-ATPASE ARE INHIBITED BY \*LY333531\***

Author(s): KOWLURU RA; JIROUSEK MR; STRAMM L; ENGERMAN RL; KERN TS

Journal: DIABETES, \*1996\*, V45, S2 (MAY), P50

ISSN: 0012-1797

Language: ENGLISH Document Type: MEETING ABSTRACT

**Title: \*DIABETES\*-INDUCED DISORDERS OF RETINAL PROTEIN-KINASE-C AND  
NA,K-ATPASE ARE INHIBITED BY \*LY333531\***  
, \*1996\*

9/3,K/34 (Item 1 from file: 71)

DIALOG(R)File 71:ELSEVIER BIOBASE  
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01307669 1999025640

**Increased protein kinase C activity and expression of Casup 2sup  
+-sensitive isoforms in the failing human heart**

Bowling N.; Walsh R.A.; Song G.; Estridge T.; Sandusky G.E.; Fouts R.L.; Mintze K.; Pickard T.; Roden R.; Bristow M.R.; Sabbah H.N.; Mizrahi J.L.; Gromo G.; King G.L.; Vlahos C.J.

ADDRESS: Dr. C.J. Vlahos, Cardiovascular Research, Eli Lilly and Co,  
Indianapolis, IN 46285-0520, United States

Journal: Circulation, 99/3 (384-391), \*1999\*, United States

CODEN: CIRCA

ISSN: 0009-7322

DOCUMENT TYPE: Article

LANGUAGES: English SUMMARY LANGUAGES: English

NO. OF REFERENCES: 34

, \*1999\*

...was to determine the relative expression of PKC-1/4, -1/2, and -alpha in failed and nonfailed myocardium. Methods and Results - Explanted hearts of \*patients\* in whom dilated cardiomyopathy or ischemic cardiomyopathy was diagnosed were examined for PKC isoform content by Western blot, immunohistochemistry, enzymatic activity, and in situ hybridization...

...increased in membrane fractions from failed hearts compared with nonfailed (1021+/-189 versus 261+/-89 pmol - mgsup -sup 1 - minsup -sup 1, P<0.01). \*LY333531\*, a selective PKC-beta inhibitor, significantly decreased PKC activity in membrane fractions from failed hearts by 209 pmol - minsup -sup 1 - mgsup -sup 1 (versus...

9/3,K/35 (Item 2 from file: 71)

DIALOG(R)File 71:ELSEVIER BIOBASE

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00831394 1998049799

**Abnormalities of retinal metabolism in \*diabetes\* or experimental**

**galactosemia: V. Relationship between protein kinase C and APTases**

Kowluru R.A.; Jirousek M.R.; Stramm L.; Farid N.; Engerman R.L.; Kern T.S.

ADDRESS: R.A. Kowluru, Dept. of Ophthalmology/Visual Sci., Medical Sciences  
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Journal: Diabetes, 47/3 (464-469), \*1998\*, United States

PUBLICATION DATE: 19980000

CODEN: DIAEA

ISSN: 0012-1797

DOCUMENT TYPE: Article

LANGUAGES: English SUMMARY LANGUAGES: English

NO. OF REFERENCES: 35

**Abnormalities of retinal metabolism in \*diabetes\* or experimental**

**galactosemia: V. Relationship between protein kinase C and APTases**

, \*1998\*

...retinopathy, experimental galactosemia. We have investigated the relationship between hyperglycemia-induced abnormalities of PKC and ATPases using a selective inhibitor of beta isoform of PKC (\*LY333531\*). \*Diabetes\* or experimental galactosemia of 2 months' duration resulted in >50% elevation of PKC activity in the retina, and administration of \*LY333531\* prevented the elevation. In retinas of the same rats, the \*LY333531\* prevented hyperglycemia-induced decreases of both Nasup +-Ksup +-ATPase and calcium ATPase activities. Retinal microvessels, the main site of lesions in diabetic retinopathy, likewise showed elevated activity of PKC and inhibition of ATPases in \*diabetes\* and in experimental galactosemia, and

administration of \*LY333531\* to diabetic animals prevented these abnormalities. PKC activity in sciatic nerves, in contrast, became subnormal in \*diabetes\* and experimental galactosemia. The results suggest that \*diabetes\*-induced reductions in Nasup +-Ksup +-ATPase and calcium ATPase in the retina are mediated in large part by PKC-beta. The availability of an agent...

9/3,K/36 (Item 1 from file: 98)  
DIALOG(R)File 98:General Sci Abs  
(c) 2006 The HW Wilson Co. All rts. reserv.

03268938 H.W. WILSON RECORD NUMBER: BGSA96018938  
**Amelioration of vascular dysfunctions in diabetic rats by an oral PKC b inhibitor.**

Ishii, Hidehiro  
Jirousek, Michael R; Koya, Daisuke  
Science (Science) v. 272 (May 3 1996) p. 728-31  
SPECIAL FEATURES: bibl il ISSN: 0036-8075  
LANGUAGE: English  
COUNTRY OF PUBLICATION: United States

ABSTRACT: The vascular complications of \*diabetes\* mellitus have been correlated with enhanced activation of protein kinase C (PKC). \*LY333531\*, a specific inhibitor of the b isoform of PKC, was synthesized and was shown to be a competitive reversible inhibitor of PKC b1 and b2...

...5 nM; this value was one-fiftieth of that for other PKC isoenzymes and one-thousandth of that for non-PKC kinases. When administered orally, \*LY333531\* ameliorated the glomerular filtration rate, albumin excretion rate, and retinal circulation in diabetic rats in a dose-responsive manner, in parallel with its inhibition of...

DESCRIPTORS:  
\*Diabetes\* mellitus...  
\*1996\*

9/3,K/37 (Item 1 from file: 135)  
DIALOG(R)File 135:NewsRx Weekly Reports  
(c) 2006 NewsRx. All rts. reserv.

0000035912 (USE FORMAT 7 OR 9 FOR FULLTEXT)  
**"Basic Fibroblast Growth Factor Induces Expression of VEGF Receptor KDR Through a Protein Kinase C and p44/p42 Mitogen-Activated Protein Kinase-Dependent Pathway."**  
Angiogenesis Weekly, July 12, 1999, p.16-17

DOCUMENT TYPE: Research News LANGUAGE: English  
RECORD TYPE: FULLTEXT  
WORD COUNT: 422

TEXT: According to the authors' abstract of an article published in \*Diabetes\*, "Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are angiogenic molecules whose combined mitogenic activity is potently synergistic. However, the molecular mechanism...

...that inhibited bFGF-induced MAPK phosphorylation 100%, suggesting that pathways in addition to MAPK might also be involved. Inhibitors of the beta isoform of PKC (\*LY333531\*), protein kinase A (PKA) (H89), and phosphatidylinositol (PI) 3 kinase (wortmannin) had no significant effect.

These data suggest that bFGF stimulates KDR expression through a...  
...LP Aiello, Joslin Diabet Ctr, Beetham Eye Inst, 1 Joslin Pl, Boston, MA  
02215 USA. For subscription information for this journal, contact the  
publisher: Amer \*Diabetes\* Assoc, 1660 Duke St, Alexandria, VA 22314 USA.  
(Authors) Hata, Y.; Rook, S.L.; Aiello, L.P. (Journal) \*Diabetes\*, May  
1999;48(5):1145-1155.

\*1999\*

9/3,K/38 (Item 1 from file: 155)  
DIALOG(R)File 155:MEDLINE(R)  
(c) format only 2006 Dialog. All rts. reserv.

12523229 PMID: 10470381

**Enzymatic rationale and preclinical support for a potent protein kinase C  
beta inhibitor in cancer therapy.**

Teicher B A; Alvarez E; Mendelsohn L G; Ara G; Menon K; Ways D K  
Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN  
46285, USA.

Advances in enzyme regulation (ENGLAND) \*1999\*, 39 p313-27, ISSN  
0065-2571--Print Journal Code: 0044263

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

...\*1999\*,

The macrocyclic bisindolylmaleimide, \*LY333531\* , selectively inhibits  
protein kinase C beta 1 and beta 2 isoforms with an approximate IC50 of 5  
nanomolar. The efficacy of \*LY333531\* administered alone and in combination  
with cytotoxic cancer therapies in models of non-small cell lung carcinoma  
and brain tumors was determined in vivo. In the Lewis lung carcinoma,  
administration of \*LY333531\* enhanced the activity of paclitaxel and  
fractionated radiation and, to a lesser degree, carboplatin and  
gemcitabine. In the human T98G glioblastoma multiforme xenograft, the  
addition of \*LY333531\* to \*treatment\* with carmustine (BCNU) resulted in  
enhanced tumor response in a nodule grown subcutaneously and increased  
life-span in animals bearing an intracranial tumor from 37 days in the  
control animals to 64 days in the BCNU \*treated\* animals, and to 104 days  
in the \*LY333531\* plus BCNU \*treated\* animals with 4 out of 5 animals being  
long-term survivors.

9/3,K/39 (Item 1 from file: 399)  
DIALOG(R)File 399:CA SEARCH(R)  
(c) 2006 American Chemical Society. All rts. reserv.

135014147 CA: 135(2)14147w JOURNAL

**Impact of PKC .beta. inhibitor on diabetic complications**

AUTHOR(S): Nawata, Hajime; Inoguchi, Toyoshi; Ishii, Hidehiro; Kunisaki,  
Makoto; Yamauchi, Teruaki; Umeda, Fumio

LOCATION: Department of Medicine and Bioregulatory Science, Graduate  
School of Medical Sciences, Kyushu University, Fukuoka, Japan, 812-8582

JOURNAL: Int. Congr. Ser. DATE: 2000 VOLUME: 1209, PAGES: 61-65

CODEN: EXMDA4 ISSN: 0531-5131 LANGUAGE: English PUBLISHER: Elsevier  
Science B.V.

9/3,K/40 (Item 2 from file: 399)

DIALOG(R)File 399:CA SEARCH(R)  
(c) 2006 American Chemical Society. All rts. reserv.

**133037993 CA: 133(4)37993s JOURNAL**

**Amelioration of accelerated diabetic mesangial expansion by treatment with a PKC .beta. inhibitor in diabetic db/db mice, a rodent model for type 2 diabetes**

AUTHOR(S): Koya, Daisuke; Haneda, Masakazu; Nakagawa, Hiroko; Isshiki, Keiji; Sato, Haruhisa; Maeda, Shiro; Sugimoto, Toshiro; Yasuda, Hitoshi; Kashiwagi, Atsunori; Ways, D. Kirk; King, George L.; Kikkawa, Ryuichi

LOCATION: Third Department of Medicine, Shiga University of Medical Science, Shiga, Japan, 520-2192

JOURNAL: FASEB J. DATE: 2000 VOLUME: 14 NUMBER: 3 PAGES: 439-447

CODEN: FAJOEC ISSN: 0892-6638 LANGUAGE: English PUBLISHER: Federation of American Societies for Experimental Biology

**9/3,K/41 (Item 3 from file: 399)**

DIALOG(R)File 399:CA SEARCH(R)  
(c) 2006 American Chemical Society. All rts. reserv.

**125075324 CA: 125(7)75324s JOURNAL**

**(S)-13-((Dimethylamino)methyl)-10,11,14,15-tetrahydro-4,9:16,21-dimetheno-1H,13H-dibenzo(e,k)pyrrolo(3,4-h)(1,4,13)oxadiazacyclohexadecene-1,3(2H)-dione (LY333531) and Related Analogs: Isoenzyme Selective Inhibitors of Protein Kinase C.beta.**

AUTHOR(S): Jirousek, Michael R.; Gillig, James R.; Gonzalez, Cecile M.; Heath, William F.; McDonald, John H., III; Neel, David A.; Rito, Christopher J.; Singh, Upinder; Stramm, Lawrence E.; et al.

LOCATION: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285, USA

JOURNAL: J. Med. Chem. DATE: 1996 VOLUME: 39 NUMBER: 14 PAGES: 2664-2671 CODEN: JMCMAR ISSN: 0022-2623 LANGUAGE: English

**9/3,K/42 (Item 1 from file: 35)**

DIALOG(R)File 35:Dissertation Abs Online  
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01611141 ORDER NO: AAD98-10951

**MECHANISMS REGULATING INSULIN SENSITIVITY IN SKELETAL MUSCLE (PROTEIN KINASE C, ALKALINE PHOSPHATASE, EXERCISE)**

Author: ZHOU, QIAN

Degree: PH.D.

Year: \*1997\*

Corporate Source/Institution: EAST CAROLINA UNIVERSITY (0600)

Source: VOLUME 58/09-B OF DISSERTATION ABSTRACTS INTERNATIONAL.  
PAGE 4786. 173 PAGES

Year: \*1997\*

...and glucose transport were impaired in skeletal muscle of obese Zucker rats. Similar defects were also found in insulin-resistant human skeletal muscle. Alkaline phosphatase \*treatment\*, which removes all the phosphates from the insulin receptor, increased the depressed kinase activity of the insulin receptors isolated from both insulin-resistant human and rat skeletal muscles. Further study demonstrated that GF 109203X, a PKC specific inhibitor, increased insulin-stimulated glucose transport and insulin receptor tyrosine phosphorylation. Likewise \*treatment\* of obese Zucker rats with \*LY333531\* (a PKC $\beta$  specific inhibitor)

suggested that PKC $\beta$  isozyme is involved in the induction of insulin resistance in white muscle of insulin-resistant obese...

...insulin-resistant skeletal muscle of obese Zucker rats, since the insulin-stimulated IRS-1 tyrosine phosphorylation or PI 3-kinase activity was not increased by \*LY333531\* \*treatment\*.

Finally, muscle contraction, which had previously been shown to restore insulin responsiveness in insulin-resistant skeletal muscle of obese Zucker rats, was found to have...

9/3,K/43 (Item 1 from file: 149)  
DIALOG(R)File 149:TGG Health&Wellness DB(SM)  
(c) 2006 The Gale Group. All rts. reserv.

01781574 SUPPLIER NUMBER: 20963335 (USE FORMAT 7 OR 9 FOR FULL TEXT)  
**Pathogenesis, prevention, and \*treatment\* of diabetic nephropathy.(part 1)**  
Cooper, Mark E.  
The Lancet, v352, n9123, p213(1)  
July 18,  
1998  
PUBLICATION FORMAT: Magazine/Journal; Refereed ISSN: 0099-5355  
LANGUAGE: English RECORD TYPE: Fulltext; Abstract TARGET AUDIENCE:  
Professional  
WORD COUNT: 4143 LINE COUNT: 00353

**Pathogenesis, prevention, and \*treatment\* of diabetic nephropathy.(part 1)**

ABSTRACT: Early diagnosis and control of \*diabetes\* is important in preventing the development of diabetic nephropathy. Poor glucose control, excessive blood pressure, and other factors contribute to kidney disease associated with \*diabetes\*. Dietary modification to maintain stable blood glucose levels and reduce protein intake, and tight glucose control by insulin injection and other pharmacologic methods can prevent kidney damage. Antihypertensive and hypoglycemic drugs contribute to management of \*diabetes\* and prevention of the associated complications.

TEXT:

...enabling investigation of the role of these processes in the pathogenesis of diabetic nephropathy and potentially to provide new therapeutic approaches for the prevention and \*treatment\* of diabetic nephropathy. Haemodynamic factors to consider include systemic hypertension, intraglomerular hypertension, and the role of vasoactive hormones, such as angiotensin II. The mainstay of...

Proteinuria was first recognised in \*diabetes\* mellitus in the late 18th century and 40 years later Bright postulated that this form of renal disease was specific to \*diabetes\*. The disorder, diabetic nephropathy, was further clarified by Kimmelsteil and Wilson in the 1930s when they described the classic lesions of nodular glomerulosclerosis associated with proteinuria and hypertension. By the early 1950s, it had become apparent that nephropathy was not a rare complication of \*diabetes\* -- up to 50% of \*patients\* who have had \*diabetes\* for more than 20 years seen at The Joslin Clinic, Boston, had this complication.

Diabetic nephropathy is now the principal cause of end-stage renal failure in the western world. Renal disease remains a major cause of morbidity and mortality for \*patients\* with insulin-dependent \*diabetes\* mellitus (IDDM) and is becoming an increasingly important clinical problem in non-insulin-dependent \*diabetes\* mellitus (NIDDM). Indeed, because the prevalence of NIDDM is at least five-fold higher than IDDM, this form of \*diabetes\* now contributes to at least 50% of \*patients\* who have \*diabetes\* in end-stage renal-failure programmes.

Natural history

It is possible to assess \*patients\* with IDDM even before the onset of overt renal disease, and so clinical investigators have been able to characterise in detail the development of diabetic renal disease. The classification of nephropathy by Mogensen into several distinct phases can, in general, be used for both forms of \*diabetes\*. Initial changes include glomerular hyperfiltration and hyperperfusion -- functional changes that are seen more often in IDDM than in NIDDM. The importance of these functional changes...

...a urinary albumin-excretion rate of 20-200 g/min. Microalbuminuria is predictive of the development of overt proteinuria, particularly in IDDM. Longitudinal studies in \*patients\* with IDDM have suggested that in the transition from normoalbuminuria to microalbuminuria there is a modest rise in blood pressure of about 3 mm Hg per year, best detected by ambulatory blood-pressure monitoring. In the microalbuminuric phase significant glomerular injury can be seen on renal-biopsy samples, although for \*patients\* with NIDDM the pattern is more heterogeneous, suggesting a more complex pathogenesis than in IDDM. Microalbuminuria is commonly associated with other diabetic complications as well as with cardiovascular disease, particularly in \*patients\* with NIDDM (panel 1). Many explanations have been suggested for the association of microalbuminuria with cardiovascular disease such as endothelial dysfunction, hypertension, abnormalities in lipid...

...stage renal-failure programmes such as dialysis or transplantation.

#### Pathophysiology

There may be an interplay of metabolic and haemodynamic pathways in the renal microcirculation in \*diabetes\* (figure 1). Inhibitors of these pathways have increased our understanding of the underlying pathogenic pathways and have led to the development of new approaches to the \*treatment\* of diabetic nephropathy (panel 2).

Because \*diabetes\* is a state of chronic hyperglycaemia, it is probable that glucose-dependent processes are involved in diabetic nephropathy. For example, the chronic effects of glucose in inducing tissue injury may occur via the generation of advanced glycated proteins (AGE). AGE accumulate in the kidney, particularly in people with \*diabetes\* or declining renal function, or both. Aminoguanidine, an inhibitor of AGE formation, reduces accumulation of renal AGE, and also retards the development of albuminuria and mesangial expansion. Several clinical studies are in progress that focus on the role of aminoguanidine in end-stage renal disease and in diabetic \*patients\* with nephropathy, either with overt renal disease or microalbuminuria. Two separate studies, known as Action 1 and Action 2 have completed the randomisation phase and involve assessment of the effects of aminoguanidine in \*patients\* with type 1 and type 2 \*diabetes\* with overt proteinuria and impaired renal function. An alternative approach to inhibit the effects of advanced glycation involves the use of the thiazolium compound, phenacylthiazolium...

...this agent can cleave preformed AGE cross-links it may have a role in reversing AGE-mediated tissue damage and be of particular relevance in \*patients\* with \*diabetes\* and established renal disease.

Another glucose-dependent pathway, known as the polyol pathway has been implicated in the pathogenesis of diabetic nephropathy. To further explore...

...man with conflicting results. The activity of the enzyme, protein kinase C, has been reported to be increased in various diabetic tissues including the glomerulus. \*LY333531\*, an orally active inhibitor of the  $\beta$ II isoform of protein kinase C has been developed. \*LY333531\* prevents the development of hyperfiltration and albuminuria in diabetic rats. Diabetic nephropathy is commonly associated with systemic hypertension. Micropuncture studies have shown that in animal models of \*diabetes\* there is an elevation of the

intraglomerular pressure, even in the absence of systemic hypertension. These renal haemodynamic changes may be partly related to the actions of vasoactive hormones such as angiotensin II and endothelin. Whether these hormone pathways are altered in \*diabetes\* or their actions are amplified in the context of hyperglycaemia remains to be clarified. In animal models of \*diabetes\*, angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-II-receptor antagonists have been shown to reduce intraglomerular pressure. It has been suggested that since ACE inhibitors ...factors

It is likely that genetic factors play a part in the susceptibility to diabetic nephropathy. Indeed, siblings of probands with diabetic nephropathy who have \*diabetes\* have a higher incidence of renal disease. A family history of hypertension has also been associated with an increased risk of diabetic nephropathy. Some, but...

...This increased activity may occur as a result of an increase in the activation of pertussis-sensitive G proteins as has recently been reported in \*patients\* with IDDM and nephropathy. Nevertheless, the genes responsible for ion transport cannot be considered at this stage to entirely explain the genetic susceptibility to diabetic...

...gene poly-morphism may represent a genetic determinant of the renal response of an individual to inhibition of ACE. Allen and colleagues showed that in \*patients\* with IDDM there is already an increase in serum prorenin, the precursor of the active enzyme renin, before the onset of microalbuminuria. However, tests for...

...of adequate sensitivity or specificity to be used in routine clinical practice. To further explore the role of renin in the development of diabetic nephropathy, \*diabetes\* was induced in transgenic Ren 2 rats -- a rat strain generated by insertion of the mouse renin Ren 2 gene into their genome. This hypertensive strain has elevated prorenin concentrations and induction of \*diabetes\* leads to the rapid development of glomerulosclerosis, tubulointerstitial injury, and renal impairment that could be attenuated by ACE inhibition. These findings are consistent with the renin-angiotensin system, particularly at the local level, mediating renal injury in \*diabetes\*.

#### \*Treatment\*

##### Glycaemic control

In both IDDM and NIDDM, it has been shown that hyperglycaemia is a major determinant of progression of diabetic nephropathy. Several studies including the \*Diabetes\* Control and Complications Trial have indicated that intensified glycaemic control retards the rate of development of both microalbuminuria and overt proteinuria in \*patients\* with IDDM with normal albuminuria. In a Japanese study of \*patients\* with NIDDM, intensified glycaemic control was also shown to reduce the rate of development of diabetic nephropathy. However, this phenomenon of slowing the development of diabetic nephropathy by improving glycaemic control has not been as clearly shown in Europid \*patients\* with NIDDM. It is hoped that the findings of the UK Prospective \*Diabetes\* Study, due to be reported before the end of 1998, will clarify the situation in this population.

The role of intensified glycaemic control in \*patients\* with IDDM and persistent microalbuminuria or overt nephropathy remains controversial. In the \*Diabetes\* Control and Complications Trial, no advantage of intensified glycaemic control was found in the cohort of \*patients\* who had microalbuminuria at the beginning of the study. Similar findings have been observed by the Microalbuminuria Collaborative Study Group, in the UK. However, several Scandinavian studies have suggested reduced progression in \*patients\* with microalbuminuria and IDDM with intensified insulin therapy. Previously, it had been viewed that once \*patients\* with IDDM are overtly proteinuric, intensified glycaemic control plays almost no part in

retarding progression. However, several recent studies have suggested that glycaemic control has an important role in \*patients\* with IDDM and nephropathy, particularly if blood pressure is well controlled. Antihypertensive \*treatment\*

It is now over 20 years since Mogensen showed that antihypertensive \*treatment\* could attenuate the rate of decline in renal function in \*patients\* who had IDDM, hypertension, and proteinuria. Since that time there has been a striking increase in the interest in antihypertensive medication in diabetic nephropathy. A range of studies have been done which involved the use of these agents, as part of a preventive approach, in both forms of \*diabetes\*, in the presence or absence of conventionally defined systemic hypertension, and in various phases of diabetic renal disease as well as in people with normal urinary albumin excretion. Nevertheless, the appropriate therapy and the stage at which to commence \*treatment\* remains controversial (panel 3).

#### Overt nephropathy

The evidence for aggressive antihypertensive \*treatment\* in \*patients\* with IDDM, hypertension, and nephropathy is now overwhelming. It is likely ...that ACE inhibitors are particularly useful in this population with clear-cut evidence that these agents not only reduce proteinuria, but reduce the number of \*patients\* who will develop end-stage renal failure. Although ACE inhibition is clearly very useful in this population, in the collaborative study by Lewis and colleagues there was less benefit seen in the \*patients\* with serum creatinine of less than 0.15 mmol/L or normal blood pressure. These findings are consistent with an updated meta-analysis, which suggests...

...of focusing on aggressive blood-pressure reduction rather than ACE inhibition per se is suggested in a more recent study by the Collaborative Study Group. \*Patients\* with IDDM and proteinuria were randomly allocated to low or high doses of the ACE inhibitor, ramipril, with the primary aim being to achieve a...

...in albuminuria whereas the low-dose ramipril group had an increase in albuminuria. A link between reduced rates of progression and improvement in prognosis in \*patients\* with IDDM and nephropathy has been noted by Parving's group with both ACE inhibitors and conventional agents. This link is consistent with the view that the major focus for \*treatment\* in this population must be on aggressive blood-pressure reduction.

Even though ACE inhibitors may be antiproteinuric, many \*patients\* with IDDM will still have inadequately controlled blood pressure. This lack of strict blood-pressure control may be a major factor in the continued rate of decline in renal function in the captopril-\*treated\* group, albeit at a slower rate, in the Collaborative study. Diuretics should be considered as the next line of therapy, probably as an additional agent, in such \*patients\*. Other approaches to consider include dietary salt restriction, which has been shown experimentally to reduce diabetic renal injury, or newer pharmacological agents such as the dual ACE-neutral endopeptidase inhibitors. For \*patients\* with NIDDM and macroproteinuria, antihypertensive \*treatment\* has been shown to be renoprotective although the role of ACE inhibitors has not been as clearly defined as in \*patients\* with IDDM. There are now several multicentred large-scale studies in progress which are assessing the role of angiotensin II receptor antagonists in this clinical context. Several studies have confirmed that ACE inhibitors are superior to other antihypertensive agents, including the dihydropyridine calcium-channel blockers (CCB), in reducing albuminuria in \*patients\* with NIDDM who are hypertensive and have macroproteinuria. Parving's group has reported a disparity in effects on albuminuria and renal function. Whereas lisinopril was more effective than atenolol in reducing albuminuria, both agents were similar in efficacy in terms of rate of decline in glomerular-filtration rate.

#### Microalbuminuria

For \*patients\* with IDDM and microalbuminuria, even when blood pressure is normal, ACE inhibition has been clearly shown by the Microalbuminuria Captopril Study Group in a 2...

...this population with the dihydropyridine calcium antagonist, nifedipine. However, a recent Italian study has suggested that nifedipine can delay the onset of overt nephropathy in \*patients\* with IDDM who have normal blood pressure and microalbuminuria. In an 8-year placebo-controlled study, captopril prevented the development of macroproteinuria and was associated ...

...provides the first long-term evidence that appropriate timing of the start of ACE-inhibitor therapy in this normotensive population postpones, and possibly in some \*patients\* prevents, the development of overt nephropathy.

Because ACE inhibitors appear to be renoprotective for \*patients\* with IDDM and microalbuminuria and up to 40% are at risk of nephropathy, it has been suggested that ACE inhibition may be an appropriate preventive \*treatment\* in \*patients\* with IDDM and normo-albuminuria. However, in the EUCLID study, no evidence of a beneficial role for the ACE inhibitor, lisinopril, in \*patients\* with IDDM and normo-albuminuria was found. This may partly relate to the relatively short duration, of only 2 years, of the EUCLID study. ACE...

...retinopathy. These promising results now require confirmation in another appropriately designed study with retinopathy as a major end-point.

The use of antihypertensive therapy for \*patients\* with NIDDM, hypertension, and microalbuminuria has been assessed by an increasing number of investigators over the past decade. In the largest of these studies, which involved over 300 \*patients\*, the ACE inhibitor, lisinopril, reduced albuminuria over 12 months. However, nifedipine failed to significantly influence urinary albumin excretion. In normotensive \*patients\* with NIDDM and microalbuminuria several placebo-controlled studies have reported the efficacy of ACE inhibition in either reducing or preventing a rise in albuminuria over at least 4 years. However, if these findings can be extrapolated to Euroid \*patients\* with NIDDM who are, in general, older and more obese has not been fully clarified.

#### Combination therapy

The combination of a calcium antagonist with an...  
...compared the renal haemodynamic and antiproteinuric effects of a calcium antagonist, verapamil, and an ACE inhibitor, lisinopril, alone and in combination in three groups of \*patients\* with NIDDM, macroproteinuria, hypertension, and renal insufficiency. \*Patients\* \*treated\* with the combination of a calcium antagonist and an ACE inhibitor showed the greatest reduction in albuminuria. In addition, the decline in glomerular filtration rate was the lowest in the group with combination \*treatment\*. Sano and colleagues have shown that the addition of enalapril to nifedipine conferred an additional effect in decreasing albuminuria in a group of microalbuminuric \*patients\* with NIDDM. Similar findings have now been reported by other groups using the combination of an ACE inhibitor with a CCB, providing further evidence of a role for combination therapy in \*patients\* with \*diabetes\* and renal disease.

#### Cardiovascular disease

Microalbuminuria predicts not only nephropathy in \*patients\* with NIDDM but also is a strong predictor of all-cause mortality, particularly from cardiovascular disease. Therefore, the effects of these antihypertensive agents must include...

...CCB, nisoldipine, in terms of fewer cardiovascular events. In another study it was suggested that fosinopril was associated with fewer

cardiovascular events than amlodipine in \*patients\* with hypertension and NIDDM. The issue of a possible deleterious effect of the dihydropyridine class of CCB on cardiovascular events in the diabetic population has...

...CCB should not be considered as first-line antihypertensive agents in NIDDM. The findings from the HOT study suggest that the major target of antihypertensive \*treatment\* in \*diabetes\* should be reduction in blood pressure. In this study most \*patients\* received the CCB felodipine, and reduction of blood pressure was associated with fewer cardiovascular events and mortality in the diabetic subgroup. However, since lower blood...

...blood-pressure reduction alone.

#### Guidelines

It is remarkable that less than 10 years ago, an editorial in The Lancet stated that most clinicians would not \*treat\* a blood pressure of 135/90 mm Hg in a \*patient\* with IDDM who was aged 25 years. Since then, several societies have prepared consensus guidelines or position statements, previously summarised by a group of international investigators led by Mogensen, indicating that there is now enough evidence to \*treat\* \*patients\* with \*diabetes\* with even lower blood pressures, particularly in the setting of early or overt renal disease. The guidelines outlined in the sixth report of the Joint National Committee on Prevention, Detection, Evaluation and \*Treatment\* of High Blood Pressure (JNC VI) have incorporated new principles for the management of blood pressure in \*diabetes\* and have included a more aggressive programme of blood-pressure reduction aiming for a target of less than 130/85 mm Hg in \*patients\* with IDDM or NIDDM. In addition, the guidelines included a target of 125/75 mm Hg in \*patients\* with \*diabetes\* and greater than 1 g per day proteinuria.

#### Dietary protein intake

A meta-analysis examining the effects of dietary protein restriction (0.5-0.85 g kg<sup>-1</sup> day<sup>-1</sup>) in \*patients\* with \*diabetes\*, suggested a beneficial effect on glomerular filtration rate, creatinine clearance, and albuminuria. However, a large, long-term prospective study is needed to establish the safety, efficacy, and compliance with protein restriction in diabetic nephropathy. Indeed, compliance may be the major limiting factor in implementing such a dietary approach in diabetic \*patients\* with renal disease.

#### Conclusions

It is now incumbent on clinicians to carefully monitor \*patients\* with IDDM and NIDDM for evidence of early renal disease. This involves regular screening for microalbuminuria, now made more convenient by the advent of reliable...

...a rational framework for the prevention and management of diabetic nephropathy (figure 2). Indeed, several cost effectiveness studies have been reported that suggest that antihypertensive \*treatment\* and in particular ACE inhibition have life-saving effects as well as considerable economic savings. However, these studies have generally focused on \*patients\* with IDDM.

The major impediments to improving the prognosis of \*patients\* with \*diabetes\* at risk of nephropathy remain defining the \*patients\* at risk of overt diabetic nephropathy, optimising glycaemic control, and implementing an effective antihypertensive \*treatment\* regimen. It is hoped that in the future these impediments will be overcome with more efficient and comprehensive screening of the diabetic population, identification of appropriate genetic or biochemical markers of risk, more extensive use of the available \*treatments\*, and the advent of new therapeutic approaches that are more effective in the prevention and management of this condition.

DESCRIPTORS: \*Diabetes\*--...

...Care and \*treatment\*;